REMARKS

Pending Claims

Claims 1, 29, 32, 34, 43-44, and 51 were withdrawn by the Examiner as being drawn to non-elected inventions.

Claim 52 is canceled.

Claims 10, 30-31, 33, and 35-42 are under consideration.

Claim 10 has been amended to incorporate the limitations of a non-elected claim (claim 1) from which it depends. No new matter has been added as a result of these amendments. Support for this amendment can be found, for example, in original claim 1. Entry of these amendments is therefore respectfully requested.

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Restriction Requirement

Applicants reiterate their traversal to the Restriction Requirement for at least the reasons already made of record. Applicants acknowledge that the Examiner has agreed to rejoin method claims upon allowance of the product claims per the Commissioner's Notice of February 28, 1996, published March 26, 1996 at 1184 O.G. 86.

Rejections under 35 U.S.C. § 101 and 35 U.S.C § 112, first paragraph

Claims 10, 30, 31, 33, 35-42, and 52 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that the 96% identity of SEQ ID NO:5 to a known protein (mouse MA-3) is insufficient to impute the activities of MA-3 to Applicants' polypeptide of SEQ ID NO:5.

The Examiner cites numerous references in order to assert two points. The first is, that the "literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities" (Office Action, p. 5). The Examiner's second point is, that "function cannot be predicted based solely on structural similarity to a protein found

in the sequence databases" (Office Action, p. 6).

The cited references fail to provide support for the Examiner's position, as explained in detail below (see Section IIA., pp. 11-13).

The Examiner further suggests that the Northern analysis data (specification at p. 17, lines 21-24) seems to be unrelated to the proposed utility of using APOP-3 in the diagnosis of conditions associated with expression of APOP-3.

Applicants' respectfully disagree. These data provide evidence for the use of APOP-3 in the diagnosis of the various disorders. These data are essentially a catalog of cDNA libraries from various cell lines and tissues which express APOP-3. These results indicate the types of tissues, cell lines or disease states in which APOP-3 is expressed and provide a basis for the use of APOP-3 in diagnosis, for example, of related diseases.

The rejection of claims 10, 30, 31, 33, 35-42, and 52 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as protein associated with cell proliferation, abbreviated as APOP-3, is a polypeptide sequence encoded by a gene that is expressed in thymus and apoptosis-inducible cell lines including thymocytes, T cells, B cells, and pheochromocytoma of mice. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. APOP-3 is, in that regard, homologous to mouse MA-3, a protein expressed in cells undergoing apoptosis. In particular, the two polypeptides share more than 96% sequence identity over 469 amino acid residues.

This is more than enough homology to demonstrate a reasonable probability that the utility of MA-3 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner *et al.*, Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998) (Exhibit F).

Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to MA-3 is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this brief the Declaration of Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 12).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, a person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device

> must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office

bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Association with apoptosis and expression in apoptosis-inducible cell lines are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this paper. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed APOP-3 is functionally related to mouse MA-3, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the claimed polypeptide shares more than 96 % sequence identity over all of its 469 amino acid residues with MA-3. This is more than enough homology to demonstrate a reasonable probability that the utility of MA-3 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998). Given homology

in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to MA-3 is, accordingly, very high.

The Examiner must accept the Applicants' demonstration that the homology between the claimed invention and MA-3 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, the Examiner has not shown that these difficulties apply in this case. Moreover, none of these references suggest that functional homology cannot be inferred by a reasonable probability in this case.

For example, Smith and Zhang (1996) discuss the pitfalls of annotating *multi-domain* proteins. The authors assert that errors in annotation can occur if a multi-domain protein is annotated based on a *single* domain without regard for the other domains. In Applicants' case, SEQ ID NO:5 can be aligned with MA-3 over the *entire* length of *both* sequences, resulting in a 96% identity. This is *not* a case in which annotation was based on a single domain.

The Examiner goes on to cite several references (Bork (2000); Doerks *et al.* (1998); Brenner (1999); and Bork *et al.* (1996)) which question the reliability of the annotation contained in various public databases that is obtained, for example, through the use of automated systems to annotate sequences computationally. Applicants respectfully point out that the protein with which SEQ ID NO:5 shares 96% identity was cloned *experimentally* (Shibahara *et al.*, Gene 166:297-301, 1995) rather than by the automated processes described in these references. Thus the pitfalls described in these references are avoided.

In another reference, Skolnick and Fetrow (2000) in describing a 3-D structure-based method for prediction of protein function recognize that "[t]he sequence-to-function is the most commonly used function-prediction method." The Examiner has provided no evidence suggesting that such a sophisticated method is required in a case in which two sequences align over the entire length of both sequences with 96% identity.

The Examiner further cites several specific examples in which members of a gene family

have different functions, however, none of these examples pertain to the APOP protein family of the present case. The Examiner cites Tischer *et al.* (U.S.Patent 5,194,596), Benjamin *et al.* (1998), and Vukicevic *et al.* (1996), Massague (1987), Pilbeam *et al.* (1993), and Kopchick *et al.* (U.S. patent 5, 350, 836) as support to doubt Applicants asserted utility. Importantly, all of these documents fail to ***specifically*** support the outstanding rejection because none of them are specifically relevant to the APOP protein family.

The Examiner cites Tischer *et al.* and Benjamin *et al.* as disclosing that VEGF and PDGF have opposite mitogenic activities. Applicants respectfully point out that the sequence homology between VEGF and the PDGF A and B chains is quite low, with little more than the conserved cysteine residues being conserved between the sequences (see Figures 4A, 4B, and 7 of Tischer). The homology is far less than the 96% identity for APOP-3 and mouse MA-3. That VEGF and PDGF do not share the same function is therefore hardly surprising, and does not in any way imply that APOP-3, with far greater homology to mouse MA-3, would not share the function of these proteins.

The Examiner cites Massague and Vukicevic *et al.* as disclosing that related members of the TGF family of proteins have different functions. Applicants note that the different members of the TGF family have from 22-70% sequence identity (and that the most closely related members are subunits of the same heterodimeric protein, not separate proteins with different functions) (Massague, p. 437, col. 1; and Figure 1). In all cases the homology is lower than that observed between APOP-3 and MA-3 (96%). These references disclosing differing functions in family members much less closely related in sequence than APOP-3 and mouse MA-3 would not serve to make one of ordinary skill in the art reasonably doubt that APOP-3 and mouse MA-3 would have similar functions.

The Examiner cites Pilbeam as allegedly disclosing two structurally closely related proteins, PTH and PTHrP, which can have opposite effects on bone resorption. The Examiner however, has ignored that "[t]here is strong homology of PTHrP with PTH only in the amino-terminal domain" (Pilbeam, p. 717, col. 2) and that N-terminal fragments of both proteins in fact have similar biological activities (Pilbeam, p. 717, col. 2). It is only when the non-homologous C-terminal regions are added that the different activities emerge. Thus this reference supports Applicants' arguments that homologous protein sequences have similar functions.

The Examiner cites Kopchick *et al.* as disclosing antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid. Applicants respectfully point out that these mutants all involve substitutions of a specific amino acid that was conserved in all species studied, from fish to humans (Kopchick, column 7, lines 5-8). This residue was also identified as essential for function based on structural analysis showing a cleft at that point in the structure, which was eliminated by substitutions with larger amino acids (Kopchick, column 9, lines 21-34). The effects of a mutation deliberately engineered so as to alter an essential functional residue are irrelevant to the question of whether a naturally-occurring sequence retains the function of its homolog, as is the case here.

In sum, none of these references contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. However, Applicants again emphasize that the applicable standard is not, proof to ***certainty***, but rather proof to ***reasonable probability***.

B. The uses of APOP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application, United States patent application 09/894,657 filed on June 28, 2001 (hereinafter "the Hillman '657 application") is a divisional of, and claims priority to, United States patent application 09/410,372 filed on September 30, 1999, which is a divisional of United States patent application 08/985,335 filed on December 4, 1997 (hereinafter "the Hillman '335 application"), all having essentially the same specification, with the exception of corrected typographical errors and reformatting changes.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Hillman '335 application on December 4, 1997 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-12). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Hillman '335 application ... and other related pre-December 1997 publications, persons skilled in the art on December 4, 1997 clearly would have understood the Hillman '335 application to disclose the SEQ ID NO:5 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶10)
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> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:5 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating disorders associated with abnormal cell proliferation and apoptosis for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Exhibit A):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Exhibit A), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Exhibit B); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Exhibit C).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir

paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Exhibit D) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of

utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific, substantial, and credible" utilities. (Office Action at p. 8.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its 96 % homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § [II.A]., *supra*, the literature cited by the Examiner is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

In the present case, the Examiner contended that the degree of amino acid identity among APOP-3 and a mouse protein associated with apoptosis (MA-3) is insufficient to establish that APOP-3 is a homolog of MA-3 and thus share the same utilities. The Examiner attempted to support this assertion with the teachings of Bowie *et al.* (Science (1990) 247:1306-1310). However, this reference fails to support the outstanding rejections.

Applicants submit that the teachings of Bowie *et al.* are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of APOP-3 based on amino

acid sequence homology to MA-3. Careful review of this reference reveals that the teachings of Bowie *et al.* are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the claimed polypeptide, Bowie *et al.* teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie *et al.*, page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As taught by Bowie *et al.*, proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among Applicants' claimed polypeptide and known apoptosis associated proteins are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would further conclude that the level of conservation observed between Applicants' claimed polypeptide and MA-3 is indicative of a common function, and hence, common utility, among these proteins.

In further support of this assertion, Applicants direct the Examiner's attention to the enclosed reference by Brenner *et al.* ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner *et al.* have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner *et al.*, pages 6073 and 6076.) As shown in Figures 8A and 8B and as reported in the specification, SEQ ID NO:5 and a mouse apoptosis-

associated protein (MA-3; GI 1384078) share 96% identity over 469 amino acids, thus more than meeting the criteria of Brenner *et al.* Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner *et al.* further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner *et al.*, page 6076.) SEQ ID NO:5 and MA-3 (GI 1384078) also meet these criteria, as the entire length of SEQ ID NO:5 shows ungapped identity to MA-3 (GI 1384078) at 453 out of 469 residues, corresponding to 96% sequence identity. Therefore, SEQ ID NO:1 and MA-3 (GI 1384078) share sequence identity that exceeds the thresholds proposed by Brenner *et al.* Thus, SEQ ID NO:5 is a true MA-3 homolog by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:5 to possess the evolutionarily conserved structural and functional characteristics of MA-3. Hence, the "reasonably correlation" standard as set by case law has been met.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene

> probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was
insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a

particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

SUMMARY

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those

facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Written description rejection under 35 U.S.C § 112, first paragraph

Claims 10, 30, 31, 33, 35-42, and 52 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not adequately described in the specification, asserting that the claims are drawn to a large genus of molecules. The claims, as currently amended, are drawn to antibodies which specifically bind polypeptides having SEQ ID NO:5. Thus, the rejection has been rendered moot. Withdrawal of this rejection is therefore, respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 10, 30, 31, 33, 35-42, and 52 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Claim 10 has been amended to include the limitations of claim 1. No new matter has been added by these amendments. Claim 10, as currently amended,

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[1] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

is now in independent form and thus the rejection has been rendered moot. Withdrawal of this rejection is therefore, respectfully requested.

Rejection under 35 U.S.C. § 102(a)

Claims 10, 35, 36, and 52 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Matsuhashi *et al.* (Res. Comm. in Biochem. Cell. & Mol. Biol. 1:109-20, 1997). As recited by the Examiner 102(a) bars issuance of a patent when "the invention be know or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent." The Matsuhashi reference, however, is not prior art. Attached is Exhibit E, which demonstrates the date of invention of SEQ ID NO:5 as was at least as early as 16 October 1996. This antedates the Matsuhashi reference, thus removing it as prior art. Therefore, the Examiner has failed to make out a prima facie case because she has not cited a single prior art reference that discloses all of the elements and limitations of Applicants' present claims. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 10, 30-31, 33, 35-42, and 52 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuhashi *et al.*, Onishi *et al.*, or Shibahara *et al.* in view of Campbell, Harlow and Lane, Bird *et al.*, U.S. Patent No. 6,180,370, or Huse *et al.*, in various combinations. The claims, as currently amended, recite an antibody which binds specifically to a polypeptide of SEQ ID NO:5. The Examiner admits, at pp. 13-15, that none of the references teach SEQ ID NO:5. Therefore, as each and every element and limitation of the claims as they are currently pending is not taught by the combination of any of the cited references, the rejections under 35 U.S.C. §103(a) are improper. Applicants respectfully request that these rejections be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Please charge Deposit Account No. **09-0108** in the amount of **$420.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,

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Attachments:

Exhibit A. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999).

Exhibit B. Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999).

Exhibit C. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).

Exhibit D. Dr. Cynthia Afshari e-mail to an Incyte employee, dated July 3, 2000

Exhibit E. Print-out of Clone Information for SEQ ID NO:5 (Project ID 2518507).

Exhibit F. Steven E. Brenner *et al*, Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, PNAS 95:6073-8 (1998).